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Ambient Water Quality Criteria 2,3,7,8-Tetrachlorodibenzo-P-Dioxin

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2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Ambient Water Quality Criteria

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Washington, D.C.

CRITERION DOCUMENT

2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

CRITERIA

Aquatic Life

For freshwater aquatic life, no criterion for 2,3,7,8-tetrachlorodibenzo-p-dioxin can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

For saltwater aquatic life, no criterion for 2,3,7,8-tetrachlorodibenzo-p-dioxin can be derived using the Guidelines, and there are insufficient data to estimate a criterion using other procedures.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to TCDD through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of TCDD estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of 4.55×10^{-7} µg/l, 4.55×10^{-8} µg/l, and 4.55×10^{-9} µg/l, respectively.

BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality sta, ...

KEYWORDS: *Water quality, *Toxicology, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Dioxins, *Dibenzodioxin/tetrachloro.

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Introduction

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a contaminant inadvertently formed during the production of 2,4,5-trichlorophenol (2,4,5-TCP) from 1,2,4,5-tetrachlorobenzene (Milnes, 1971; Kimmig and Schulz, 1959; Firestone, et al. 1972). 2,4,5-TCP represents the major chemical feedstock for the production of numerous herbicides and TCDD has been reported to be a contaminant of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-T esters, Silvex, 2,4-dichlorophenoxyacetic acid (2,4-D), and clophen (Buser and Bosshardt, 1974; Courtney, et al. 1970; Edmunds, et al. 1973; Zitko and Choi, 1971). It has also been reported that TCDD may be formed during the burning of vegetation treated with 2,4,5 (Buu-Hoi, et al. 1971a,b).

A survey prepared in 1974 for the Council on Environmental Quality indicates the wide range and vast quantity of TCP-related herbicides (2,4-D and 2,4,5-T) used by both the private and public sectors (Anonymous, 1974). It has been estimated that approximately 2 million acres in the United States have been treated for weed control on one or more occasions with approximately 15 million pounds of TCDD contaminated 2,4,5-T, 2,4-D, or combinations of the two.

TCDD is a symmetrical, nearly planar molecule with the empirical formula $C_{12}H_4Cl_4O_2$. Each of the four chlorine atoms is indistinguishable from one another (Poland and Glover, 1973). Other chlorinated dibenzodioxins have been identified and isomers containing from one to eight chlorine

atoms in various isomeric forms are possible although TCDD is the most toxic of all chlorodibenzodioxins (Anonymous, 1973; Kimbrough, 1974).

Characteristically, TCDD is a white crystalline solid with a melting point range of 302 to 305 degrees C (Sparschu, et al. 1971; Elvidge, 1971). Decomposition begins at 500 degrees C and is virtually complete within 21 seconds at a temperature of 800 degrees C (Stehl, et al. 1973). TCDD has a molecular weight of 321.98 and is not volatile (Kearney, et al. 1973). TCDD is lipophilic, exhibiting a high degree of solubility in fats, oils, and other relatively nonpolar solvents, and is only slightly soluble in water (0.2 to 0.6 µg/l) (Kearney, et al. 1973; Baughman and Meselson, 1973; Jackson, 1972). The partition coefficient of TCDD in a water:hexane system has been reported to be 1,000 (Matsumura and Benezet, 1973).

TCDD is considered to be a highly stable compound which can be degraded only by temperatures in excess of 500 degrees C or by irradiation with UV light under certain conditions.

TCDD is one of the most toxic substances known. It exhibits a delayed biological response in many species and is highly lethal at low doses to aquatic organisms, birds, and mammals, including man. It has been shown to be acneigenic, embryolethal, teratogenic, mutagenic (in certain organisms), carcinogenic, and to affect the immune responses in mammals. TCDD has also been shown to persist for 10 years after application to soils and to bioaccumulate in aquatic organisms by factors as high as 8,000-fold. These

findings in conjunction with the wide distribution of contaminated products, lead to the conclusion that TCDD represents a potential hazard to both aquatic and terrestrial life.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The compound 2,3,7,8-tetrachlorodibenzo-p-dioxin has been studied in model ecosystmes with a variety of plant, invertebrate, and fish species. Exposures of fish and invertebrate species to 2,3,7,8-tetrachlorodibenzo-p-dioxin in the water, food, and by intraperitoneal injection have demonstrated a variety of adverse effects over time at very low concentrations. No standard acute or chronic toxicity tests have been conducted with this compound.

Miscellaneous

Isensee and Jones (1975) conducted a model ecosystem study with 2,3,7,8-tetrachlorodibenzo-p-dioxin and observed bioconcentration factors between 3,600 and 26,000 over a 3- to 31-day period (Table 1). The accuracy of these factors is unknown due to the nature of these tests in which the water concentrations vary with time. However, it is obvious that this compound has a high affinity for the tissues of aquatic species.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on survival, feeding, reproduction, and other functions have been demonstrated at very low concentrations (Table 1). The mortality observed by Miller, et al. (1973) among coho salmon is unique. They exposed coho salmon to an aqueous concentration of 0.000056 ug/l for 96 hours under static conditions and then transferred the fish to control water. After 60 days there was 12 percent mortality compared to 2 percent mortality among the control fish. Coho salmon exposed to 0.056 ug/l for 24 hours or longer were all dead within 40 days. After 60 days observation there was 55 percent mortality of those fish exposed to 0.0056 ug/l.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

Final Fish Acute Value = not available

Final Invertebrate Acute Value = not available

Final Acute Value = not available

Final Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = not available

Residue Limited Toxicant Concentration = not available

Final Chronic Value = not available

0.44 x Final Acute Value = not available

Although few data are available for this compound, sufficient information exists to indicate a potential great environmental hazard. A variety of aquatic organisms bioconcentrated 2,3,7,8-tetrachlorodibenzo-p-dioxin to 20,000 times or more. When coho salmon were exposed for 96 hours and placed in uncontaminated water for observation over a 60-day period, there was 12 percent mortality of those fish exposed to 0.000056 ug/l.

No freshwater criterion can be derived for 2,3,7,8-tetrachlorodibenzo-p-dioxin using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

Table 1. Other freshwater data for 2,3,7,8-tetrachlorodibenzo-p-dioxin

Organism	Test Duration	Effect	Result (µg/l)	Reference
Alga, *Oedogonium cardiacum*	31 days	Bioconcentration factor = 9,000	-	Isensee & Jones, 1975
Duckweed, *Lemna minor*	31 days	Bioconcentration factor = 3,600	-	Isensee & Jones, 1975
Cladoceran, *Daphnia magna*	31 days	Bioconcentration factor = 26,000	-	Isensee & Jones, 1975
Snail, *Physa sp.*	31 days	Bioconcentration factor = 20,000	-	Isensee & Jones, 1975
Snail, *Physa sp.*	1,152 hrs	Reduced reproduction	0.200	Miller, et al. 1973
Worm, *Paranis sp.*	1,176 hrs	Reduced reproduction	0.200	Miller, et al. 1973
Mosquito (larva), *Aedes aegypti*	408 hrs	No effect	0.200	Miller, et al. 1973
Coho salmon, *Oncorhynchus kisutch*	96 hrs*	12% mortality	0.000056	Miller, et al. 1973
Rainbow trout, *Salmo gairdneri*	672 hrs	Feeding decline	0.0023** (in food)	Miller, et al. 1973
Rainbow trout, *Salmo gairdneri*	30 days	Mortality, feeding decline, weight loss, fin erosion, fungal growth, liver degeneration	2,300** (in food)	Hawkes & Norris, 1977
Channel catfish, *Ictalurus punctatus*	6 days	Bioconcentration factor = 8,000	-	Isensee & Jones, 1975
Mosquitofish, *Gambusia affinis*	3 days	Bioconcentration factor = 25,000	-	Isensee & Jones, 1975
Guppy, *Poecilia reticulata*	120 hrs	Mortality	0.1	Norris & Miller, 1974

Table 1. (continued)

Organism	Test Duration	Effect	Result (ug/l)	Reference
Guppy, *Poecilia reticulata*	120 hrs	Feeding decline, skin discoloration, fin necrosis, mortality	10	Miller, et al. 1973
American bullfrog, *Rana catesbeiana*	35 days	No mortality for larva and adults	1,000** (interperitoneal) injection	Beatty, et al. 1976

* Mortality occurred during 60-day period after one 96-hour exposure.

**Result expressed in mg/kg.

SALTWATER ORGANISMS

Introduction

No data on the effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin on saltwater aquatic life are available.

CRITERION FORMULATION

Saltwater - Aquatic Life

No saltwater criterion can be derived for 2,3,7,8-tetrachlorodibenzo-p-dioxin using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available, and there are insufficient data to estimate a criterion using other procedures.

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2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN

Human Health Effects Section

EXPOSURE

Water. The amount of human exposure that can be directly attributed to drinking water alone is difficult to determine. However, a National Academy of Science document states that no 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) has ever been detected in drinking water with limits of detection in the parts per trillion (ppt) range (National Research Council, 1977). Harvey (1973) listed the solubility of TCDD as 0.2 parts per billion (ppb) in water and Helling, et al. (1973) indicated that this is one major factor affecting mobility. Helling (1971), Kearney, et al. (1972) and Helling, et al. (1973) found that TCDD tended to remain on or near the surface of the soil and did not move. Kearney, et al. (1972) concluded that underground water supplies would probably not be contaminated with TCDD since vertical movement did not occur in their soil samples.

Food. The occurrence of TCDD in food could result from (1) accidental spraying of plant crops; (2) contaminated forage; or (3) food chain magnification.

Although 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) can no longer be used for food crops, it could possibly reach these crops accidentally. However, studies with either the seeds or the mature plants of soybeans or oats showed that TCDD was neither absorbed by the seeds after spraying nor taken up from the soil into the mature plants (Isensee and Jones, 1971; Matsumura and Benezet, 1973). When an aqueous suspension of pure TCDD was exposed to either artificial light or sunlight, photodecomposition was negligible (Crosby, et al. 1971). However, when the herbicides, Agent Orange and Esteron, containing TCDD, were exposed to light the TCDD was rapidly lost (Crosby and Wong, 1977). This loss was thought to be due principally to photochemical dechlorination. Crosby and Wong (1977) also stated about TCDD that "...opportunities for it to occur environmentally in pure form are negligible..."

Cattle feeding on contaminated forage could result in TCDD accumulation in tissues. Kocher, et al. (1978) found 3 out of 23 adipose tissue samples positive with a detection limit of from 3 to 6 ppt. These positive samples were very close to the low detection limit. The amount of TCDD to which the cattle were exposed is unknown. Studies done under the auspices of the EPA Dioxin Implementation Plan (U.S. EPA, 1978)
revealed 8 positive beef fat samples out of 67 samples from cattle in areas previously exposed to 2,4,5-T. Forty-three beef liver samples were negative. The detection limit was 10 ppt and 5 of the 8 positive fat samples were at or below this level. How much TCDD was in the forage was unstated.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms, but BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States. Since data indicate that the BCF for lipid-soluble compounds is proportional to percent lipids, BCF's can be adjusted to edible portions using data on percent lipids and the amounts of various species consumed by Americans. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey and data on the fat content of the edible portion of these species (Sidwell, et al. 1974), the relative consumption of the four major groups and the weighted average percent lipids for each group can be calculated:

Group	Consumption (Percent)	Weighted Average Percent Lipids
Freshwater fishes	12	4.8
Saltwater fishes	61	2.3
Saltwater molluscs	9	1.2
Saltwater decapods	18	1.2

Using the percentages for consumption and lipids for each of these groups, the weighted average percent lipids is 2.3 for consumed fish and shellfish.

A measured bioconcentration factor of 8.000 was obtained for 2,3,7,8-tetrachlorodibenzo-p-dioxin using channel catfish containing about 3.2 percent lipids (Isensee and Jones, 1975). Since this test only lasted 6 days, this BCF is probably lower than the steady-state value. An adjustment factor of 2.3/3.2 = 0.72 can be used to adjust the measured BCF from the 3.2

percent lipids of channel catfish to the 2.3 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 2,3,7,8-tetrachlorodibenzo-p-dioxin and the edible portion of all aquatic organisms consumed by Americans is calculated to be 8,000 x 0.72 = 5,800.

Inhalation. No data pertaining to inhalation exposure were found for TCDD. However, calculations made by the 2,4,5-T working group of EPA (U.S. EPA, 1978) indicate that a person exposed to an aerial spray of 4.0 lbs. of 2,4,5-T (containing 0.1 mg/kg TCDD) per 10 gallons of water/acre for 8 hours would receive 2×10^{-6} μg/kg of TCDD.

Dermal. The highest dermal exposure to TCDD was 0.0007 µg/kg of body weight and was calculated for a 60 kg female applying 2,4,5-T (containing 0.1 mg/kg TCDD) using a backpack sprayer (U.S. EPA, 1978). The calculations are based on a female of child bearing age in order to determine if such a person would be overexposed.

PHARMACOKINETICS

Absorption. Sprague-Dawley rats were given a single oral dose of 1.0 ug ^{14}C-TCDD/kg of body weight and monitored (Rose, et al. 1976). Absorption from the intestinal tract was estimated at about 83 percent. The response to a repeated oral dosing was also monitored and absorption was observed to be 86 percent or approximately the same as that observed for the single oral dose.

Distribution. Piper, et al. (1973) used a single oral dose of ^{14}C labeled TCDD to study distribution and excretion of TCDD in male Sprague-Dawley rats. Most of the radioactivity (53 percent) was excreted via the feces but the urine and expired air accounted for 13 percent and 2 percent respectively. Analysis of the tissues showed liver and adipose tissue to contain the highest percent of the dose per gram of tissue, 3.18 percent and 2.60 percent, respectively after 3 days.

Rose, et al. (1976) also examined the distribution of TCDD throughout the rats' body. Twenty-two days after a single oral dose, liver and adipose tissue had retained most of the ^{14}C activity, 1.26 percent and 1.25 percent per gram of tissue respectively. With repeated oral doses, the activity was again localized mainly in the liver and adipose tissue but the liver had five times as much radioactivity as did the fat. With the single oral dose, no radioactivity was detected in either the urine or expired air so most if not all of the elimination of TCDD and/or its metabolites was through the feces. With repeated oral doses, the ^{14}C activity was also excreted primarily through the feces, but significant amounts were found in the urine especially of the female rats. Male rats given 1.0 µg/kg/ day of TCDD for seven weeks excreted an average of 3.1 percent of the cumulative dose in the urine while the female rats excreted an average of 12.5 percent in the urine (Rose, et al. 1976). These results are somewhat different than Piper, et al. (1973).

Studies performed by Van Miller, et al. (1976) on rhesus monkeys and rats using tritiated TCDD showed that while rats had over 40 percent of the TCDD in the liver, the monkeys had only about 10 percent in the same organ.

Metabolism. There does not seem to be complete agreement as to whether or not TCDD is actually metabolized. Piper, et al.(1973) using oral doses concluded that, since small amounts of radioactivity were found in the urine and expired air of male rats, during the first 10 days, metabolic alteration or breakdown occurs. The study by Rose, et al. (1976) using oral doses stated that while the ^{14}C activity found in the rats' liver was unchanged TCDD, preliminary work indicated that a significant amount of radioactivity in the

rats' feces came from materials other than TCDD. Van Miller, et al. (1976) using intraperitoneal injections claimed that the slow elimination of TCDD from both rats and monkeys suggested that it was not readily metabolized. Whether the alterations in chemical form were due to microbial activity in the intestinal tract when TCDD was administered orally is unknown.

Excretion. The data reported by Piper, et al. (1973), Rose, et al. (1976) on rats and Van Miller, et al. (1976) on rats and monkeys indicated that the feces removed more of the radioactivity of labeled TCDD than did urination.

The half-life of radioactive TCDD in rats following a single oral dose was 31 $\pm$ 6 days while that following repeated oral doses was 23.7 days (Rose, et al. 1976).

EFFECTS

Acute, Subacute, and Chronic Toxicity. The 50% lethal dose (LD_{50}) for several species is shown (Table 1). The oral LD_{50} values range from 0.6 µg/kg of body weight for guinea pigs to 115 µg/kg of body weight for rabbits (Schulz, 1968; Schwetz, et al. 1973; Vos, et al. and McConnell, et al. 1978). The dermal LD_{50} for rabbits was 275 µg/kg of body weight (Schwetz, et al. 1973). Death was sometimes delayed as long as 40 days. Of the laboratory animals studied, the guinea pig was the most susceptible to the toxic effects of TCDD (Schwetz, et al. 1973; Gupta, et al. 1973).

Gupta, et al. (1973) reported that atrophy of the thymus gland was a sensitive indicator of exposure to TCDD in rats, guinea pigs and mice. The only other organ reported to have consistent microscopic changes was the liver. Rats receiving a lethal dose of TCDD had the most severe hepatic effects.

Harris, et al. (1973) also reported thymic atrophy as a common acute symptom and found that female rats actually lost weight while the male rats at the same doses only showed a 30-40 percent reduction in weight gain. Harris, et al. (1973) and Gupta, et al. (1973) showed jaundice as a common symptom.

Greig, et al. (1973) showed weight loss and mortality occurring in guinea pigs at much lower doses than those that affected the rats.

Cunningham and Williams (1972) studied the effect of single oral doses ranging from 0 to 10 μg/kg of body weight of TCDD on body weight gain and synthesis of lipids and protein. Weight gain was frequently diminished. The authors concluded that TCDD somehow restricts the transport of lipids out of the liver.

Vos, et al. (1974) found depletion of both the thymus and spleen in mice that died after being given a single oral dose of 100, 150 or 200 μg/kg of body weight of TCDD. Adema and terminal hemorrhages were frequently seen.

Schwetz, et al. (1973) reported that dogs are less sensitive to TCDD than rabbits. Symptomatology in dogs included anorexia, weight loss, dehydration, depression, emaciation, intestinal hemorrhage and alopecia.

Somewhat similar findings were made by McConnel, et al. (1978) when rhesus monkeys were given single doses of 0, 70, or 350 μg/kg of body weight of TCDD by oral gavage. Weight loss, blepharitis, facial alopecia with acneform eruptions, and anemia were present. Death occurred after the animals appeared to waste away.

Groups of male and female rats were given a dose of 0, 0.1, or 1.0 μg/kg of body weight per week by twice weekly intubation for a 28-week period and then held for 12 additional weeks by King and Roselr (1974). A certain number of these rats were killed at 2, 4, 8, 16, 28, 32 and 40 weeks. The rats did not die from the subacute exposure but did manifest toxic effects in the liver such as centrilobular fatty change and increased hepatocellular turnover. These effects were more severe in the male rats.

Vos, et al. (1974) gave oral doses of 0, 0.2, 1.0, 5.0 or 25.0 μg/kg of body weight TCDD to male mice once a week for from 2 to 6 weeks. Growth retardation occurred with the 25.0 μg/kg dose and some mice died. The three highest doses caused increased liver weight and decreased thymus weight.

Chronic studies with rats (Gupta, et al. 1973; Kociba, et al. 1976) and with guinea pigs (Gupta, et al. 1973) also showed thymic atrophy in both species but less liver damage in the guinea pigs.

Allen, et al. (1977) gave young female rhesus monkeys a diet containing 500 parts per trillion (ppt) for up to nine months. Early symptomatology included loss of facial hair and eyelashes, edema, accentuated hair follicles and dry scaly skin. Eventually, 5 of the 8 monkeys died from severe pancytopenia.

Human exposure would generally be classified as chronic since the duration of exposure is unknown in most cases. TCDD has been produced during the ~~ysis~~ of 2,4,5-trichlorophenol (TCP) or 2,4,5-T (Int. Agency. Res. Cancer, 1977).

The International Agency for Research on Cancer (1977) states in relation to occupational exposure that: "Chloracne was observed in 1952 in workers involved in the manufacture of TCP in two factories in the Federal Republic of Germany where some 60 cases were observed (W. Hergt, cited by Bauer, et al. 1961)."

Two years later, 31 cases of chloracne occurred within a few months at a factory manufacturing 2,4,5-T near Hamburg after a change in the industrial process. On this occasion the investigators were able to show that chloracne was not caused by purified TCP, and it was attributed to TCDD which occurred as a contaminant of technical TCP. Many of the exposed workers showed clinical manifestations of systemic toxicity, mainly muscular weakness, loss of appetite and weight, sleep disturbances, orthostatic hypotension, abdominal pain and liver impairment; most of them had psychopathological changes that were interpreted as a specific syndrome (Bauer, et al. 1961; Kimmig and Schulz, 1957; Schulz, 1957).

A similar outbreak of chloracne affected 60 workers at the 2,4,5-T factory of the Dow Chemical Company in Midland, Mich. in 1964 (Firestone, 1977).

Chloracne, as well as hyperlipaemia and hypercholesterolaemia, were reported in 17 workers at a factory producing TCP in France (Dugois and Colomb, 1956, 1957; Dugois, et al. 1958).

Of 29 subjects with features of chloracne working in a 2,4-D and 2,4,5-T-producing factory of the Diamond Alkali Co., Newark, N.J. 11 had increased excretion of uroporphyrins. In 3 cases a diagnosis of porphyria cutanea tarda was unquestionable; 2 of these had raised serum glutamic-oxaloacetic transaminase levels. Many of the workers, whether or not they had uroporphyrinuria, had hirsutism, hyperpigmentation, increased skin fragility and vesicobullous eruptions on exposed areas of skin (Bleiberg, et al. 1964; Firestone, 1977).

Poland, et al. (1971) re-examined all of the employees of the same factory in 1969, after the level of TCDD in the TCP had been reduced from 10-25 mg/kg to less than 1 mg/kg, and found chloracne in 13/73 workers. A number of subjects had hyperpigmentation or facial hypertrichosis, but no definite diagnosis of porphyria could be made, and only one worker had mild uroporphyrinuria. The authors suggested that chloracne and phorphyria cutanea tarda are essentially independent syndromes. About 30 percent of the workers suffered from gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pains or blood in the stools); about 10 percent of the workers had other symptoms, such as lower extremity weakness, headaches

and/or decreased auditory acuity. The severity of chloracne was associated with the degree of hypomania as measured on the Minnesota Multiphasic Personality Inventory hypomanic scale. Serum cholesterol was elevated in 10 percent of cases and serum lactic dehydrogenase in 29 percent. Seven persons (10 percent) had a white blood cell count of less than 5000/mm^3.

In a report of occupational exposure at a factory in the USSR where production of 2,4,5-T was begun in 1964, 128 workers showed skin lesions, and among 83 examined, 69 had acne. Many, especially those with severe skin lesions, also had liver impairment; 18 workers had a neurasthenic syndrome (Telegina and Bikbulatova, 1970).

Similar findings were described by Jirasek, et al. (1973, 1974), who reported 76 cases of chloracne following exposure to TCDD between 1965-1968 in a factory in Czechoslovakia producing 2,4,5-T and penthachlorophenol. Fifty-five patients were submitted to medical follow-ups for over 5 years; some had symptoms of porphyria cutanea tarda, uroporphyrinuria, abnormal liver tests (bilirubin, serum glutamic-oxaloacetic transaminase serum, glutamic-pyruvic transaminase and bromosulphthalein) and liver enlargement. The majority of patients suffered from severe neurasthenia and depressive syndrome. In 17 subjects, signs of peripheral neuropathy, especially in the lower extremities, were confirmed by electromyographic examinations. More than half of the patients showed raised blood levels of cholesterol and total lipids.

Three scientists were poisoned in the course of experimental preparation of TCDD by heating potassium trichlorophenate (Oliver, 1975). Two of them developed typical chloracne 6 and 8 weeks after exposure, respectively.

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Delayed symptoms, most likely due to TCDD, developed about 2 years after initial exposure in two of the scientists; these symptoms included personality changes, mainly loss of energy and drive, impairments of vision, taste and muscular coordination, sleep distrubances, gastrointestinal symptoms and hirsutism. Hypercholesterolaemia (in excess of 300 mg/100 ml) occurred in all 3 patients."

In relation to exposure due to accidents the International Agency for Research on Cancer (1977) further states: "The first reported cases of industrial poisoning due to the formation of TCDD in uncontrolled exothermic reactions occurring during the manufacture of TCP were seen in 1949 at a 2,4,5-T-producing factory of the Monsanto Chemical Company in Nitro, W.Va.; 228 people were affected. Symptoms included chloracne, melanosis, muscular aches and pain, fatigue, nervousness and intolerance to cold (Firestone, 1977)."

In November 1953, an accident occurred at the Badische Anilin and Soda Fabrik (BASF) factory in Ludwigshafen, Federal Republic of Germany, during the manufacture of TCP (Goldmann, 1972, 1973; Hofmann, 1957); 53 workers were affected by chloracne, 42 in a severe form; 21 of the 42 suffered consequent damage to internal organs or disturbances of the nervous system. The most relevant features were polyneuritis, sensorial impairments and liver damage. The son of one of the workers developed chloracne following contact with his father's clothes. An additional case of poisoning occurred 5 years later in a worker who was involved in repair work at the contaminated site; this worker subsequently died with necrotic pancreatitis.

In a follow-up study of these workers, Thiess and Goldmann (1977) reported that of the 53 workers exposed to TCDD in the 1953 accident, 22 were still working at the factory, 16 had retired, and 15 had died (6 while still employed at the factory and 9 in retirement). Of the 22 workers still employed, 2 still had acne of the face and scrotum, 1 had paralysis of the left leg, and 1 had permanent loss of hearing; the remaining workers were well, except for scars left by the chloracne. Of the 15 deaths, 7 were from cardiovascular disease, 2 of which were myocardial infarctus and 1, mitral stenosis, 4 from cancer, 2 from suicide, I from necrotic pancreatitis and 1 from oesophageal hemorrhage. The 16 men who had retired and were still alive were well. No abortions or miscarriages were reported in the wives of exposed workers still employed at the factory.

A similar accident occurred at the 2,4,5-T-producing factory of the Philips Duphar Company in The Netherlands in 1963 (Dalderup, 1974; Hay, 1976). Of 50 people affected, at least 10 still had skin complaints in 1976; 4 workers died within 2 years of the accident.

Five cases of chloracne were reported following an industrial accident in an Italian TCP factory (Hofmann and Meneghini, 1962).

Dugois, et al. (1968) observed 21 cases of chloracne after an accident in 1966 in a French factory producing TCP in the Grenoble region. Pain in the right hypochondrium was recorded frequently in affected workers.

A further accident occurred at the TCP-producing factory of Coalite and Chemical Products at Bolsover, Derbyshire, UK, in April 1968 (Jensen and Walker, 1972; May, 1973). Of the 14 men who were in the building during or immediately after the explosion, 10 showed some abnormality in liver function tests (increase of zinc and/or thymol turbidity and/or serum glutamic-pyruvic transaminase); however, all tests were within normal limits 10 days later, and production was started again. Within the next 7 months, 79 workers developed chloracne, with younger men being affected first; most of these workers recovered within 4-6 months. Three years later, chloracne was observed in 2 outside employees who came into contact with a tank that had been subject to the most rigorous cleaning after the accident. Although they were exposed for only one or two days, their chloracne was very persistent. In addition, the son of one and the wife of the other developed chloracne some months later.

In July 1976, an accident at the TCP-producing ICMESA factory in Meda, Italy (Bert, et al. 1976; Hay, 1976) resulted in the contamination of a large, densely populated area including the towns of Seveso, Meda, Cesano Maderno and Desio. Five days after the accident, animals began to die. Over 700 people have been evacuated from the more heavily contamined area (evacuation began two-and-a-half weeks after the accident); some 4000-5000 people still live in areas that have been found to be less heavily contaminated. The total population of the four towns involved is about 100,000 people. Hundreds of people complained of acute skin lesions and symptoms of systemic poisoning, and, by the end of October 1976, 37 cases of chloracne had been reported among the evacuated persons, mostly in children and young people. Raised serum transaminase and γ-glutamyl transferase levels were found in about 20 percent of the people living in or near the affected areas.

TCDD has been identified as the cause of an outbreak of poisoning in humans, horses and other animals in 1971 (Carter, et al. 1975; Kimbrough, et al. 1977). Exposure was related to the spraying of waste oil contaminated with TCDD on riding arenas for dust control. The most severe effects occurred in a 6-year old girl who played in the arena soil. Her symptoms included headache, epistaxis, diarrhoea, lethargy, haemorrhagic cystitis and focal pyelonephritis. Three other children and one adult who were frequently in the arena complained of skin lesions. In at least 2 of the children, the lesions described were consistent with chloracne. Intermittent arthralgias in two adults have been associated with previous exposure to the arena.

Synergistic or Antagonistic Compounds. Courtney and Moore (1971) administered 2,4,5-T containing either 0.5 and 0.06 ppm TCDD, TCDD or a combination of the two to mice. Cleft palates and kidney anomalies were found with either compound but no synergism was detected at the dose levels used when the two were combined.

No studies were found dealing with antagonistic effects of other compounds.

Teratogenicity. A study using two strains of mice and one strain of rats exposed to 2,4,5-T containing 30 ppm TCDD showed that 2,4,5-T was both teratogenic and fetotoxic to mice following oral administration of 46.4 mg/kg of body weight or more (Courtney, et al. 1970). The rats required lower doses than the mice. Both teratogenicity and fetotoxicity were found in the rats at 10 of body weight. TCDD levels of 0, 0.03, 0.125, 0.5 and 2.0, and 8.0 µg/kg of body weight/day were given orally to pregnant rats on days 6 to 15 of gestation

(Sparschu, et al. 1971). The 0.03 μg/kg of body weight level produced no effect when compared with controls. From 0.125 to 2.0 μg/kg produced fetal mortality, fetal intestinal hemmorrages, and both early and late resorptions. The incidence of these effects increased with increasing dose. Maternal mortality was not noted at either 0.03 or 0.125 μg/kg/day but at 0.5 and 2.0 μg/kg/day, the rate of maternal weight gain decreased. At 8.0 μg/kg/day, severe maternal toxicity, embryotoxicity, maternal weight loss, and early and late resorptions were evident.

The effects of TCDD on the incidence of fetal anomalies were studied in CF-1 mice by Smith, et al. (1976). Bred mice were given doses ranging from 0.001 to 3.0 μg/kg/day by gavage for 10 consecutive days starting at day 6 of gestation. The incidence of cleft palate was found to be significantly higher at dosages of 1.0 and 3.0 μg/kg of body weight/day. The incidence of bilateral dilated renal pelvis among the fetuses was significantly greater at 3.0 μg/kg of body weight/day.

Mutagenicity. Female rats were treated with a single oral dose of TCDD in amounts ranging from 30 to 500 μg/kg of body weight dissolved in dimethylsulfoxide (DMSO) or arachis oil (Greig, et al. 1973). Liver cells examined 60 days after the treatment revealed parenchymal cell alterations and many of these cells were multinucleated. There were no mitoses observed in the multinucleated cells and there were some pyknotic nuclei observed. The authors suggested that TCDD had interfered with the capacity of the liver cells to maintain proper morphology and that this led to structural disorganization and possibly cellular death. Ten mg/kg of body weight of TCDD administered as a

single intraperitoneal injection to Wistar rats produced similar effects in liver and myocardial cells (Buu-Hoi, et al. 1972a). Rabbits whose ear lobes were painted for 4 consecutive days with 0.2 ml of 20 μg/ml TCDD solution were found to have multinucleated cell formations in their livers (Kimbrough, et al. 1977).

In another study male C57Bl/6 mice (58 weeks old) were treated with a single dose of either 100, 150, or 200 μg/kg of body weight (Vos, et al. 1974). The liver cells of these mice showed enlargement. Vos, et al. (1974) treated other mice weekly with doses of 0.2 ug to 25 μg/kg of body weight of TCDD for 6 weeks had vacuolization of cell muclei, increased mitotic rate, and a polyploid chromosome number.

A dose of 10 μg/kg of body weight of TCDD dissolved in dimethylsulfoxide administered to male rats for 5 days by intubation produced no change in bone marrow preparations (Green and Moreland, 1975). TCDD dissolved in an anisole/corn oil solution (1.5 percent v/v) given in doses of 5, 10 and 15 μg/kg of body weight intraperitoneally or 20 μg/kg of body weight orally to rats also showed no chromosomal aberrations in bone marrow preparations. However, later studies by Green, et al. (1977) produced different results. The TCDD was dissolved in a mixture of one part acetone with nine parts corn oil and doses of 0.25, 0.5, 1.0, 2.0, or 4.0 μg/kg of body weight were given to male and female rats by gavage twice weekly for 13 weeks. At the end of the test period, the bone marrow was assayed for both mitotic inhibitions and chromosome aberrations. The mitotic index was unchanged regardless of dose. A statistically significant increase in the percent of cells showing chromosome

breaks was noted in both the male and female groups at the 4 μg/kg of body weight level and at the 2 μg/kg of body weight level in the male group when compared with the corresponding 0.25 μg/kg of body weight level. The authors concluded that these results were weakly positive since previous controls had shown higher percentages of breaks.

Dominant lethal studies by Khera and Ruddick (1973) showed that male Wistar rats given oral doses of TCDD of 4,8, and 12 μg/kg of body weight/day for 7 days did not get induced mutations.

Cytogenetic studies were conducted on the fetuses and the women who had become pregnant immediately before or after TCDD exposure caused by the explosion at the ICMESA 2,4,5-T factory in Seveso, Italy and had elected to abort (Tenchini, et al. 1977). Peripheral blood of the women and abortive fetal tissue were examined for both chromosome number and structural variation. No significant difference was seen in chromosome number for either maternal or fetal samples. The frequency of structural chromosome abnormalities was not significantly higher in the maternal blood samples, but the fetal tissue samples did show a higher number when compared with either the maternal samples or fibroblasts from normal adult tissue. These fetal tissue aberrations, however, were not considered to occur more frequently than would be expected to arise spontaneously in cultures of comparable cell types.

Induction of gene mutation was investigated in three bacterial systems: Escherichia coli Sd-4, Salmonella typhimurium TA 1530, and Salmonella typhimurium TA 1532 (Hussain, et al. 1972). TCDD resembles the acridine compounds

and it was therefore expected to induce frameshift mutations through intercalation with deoxyribonucleic acid (DNA). The results indicated that TCDD was indeed mutagenic via intercalation with DNA.

The response of various strains of Salmonella to 16 pesticides has been studied by Seiler (1973). TCDD only exhibited high levels of mutagenicity in the TA 1532 strain. Results from studies with strains TA 1531 and 1534 were questionable even though these strains of Salmonella generally revert through frameshift mutations. Mutations in strains G46 and TA 1530 were not observed in this study although they normally revert through frameshift mutations.

TCDD was also indicated to intercalate with DNA by its effect on the transfectivity of QB ribonucleic acid (RNA) (Kondorosi, et al. 1973).

Studies have been conducted showing that TCDD might be a dominant lethal inducing agent (Seiler, 1973; Van Miller and Allen, 1977; Murray, et al. 1977), while others have found no evidence of this effect (Khera and Ruddick, 1973).

In regard to enzyme induction the International Agency for Research on Cancer states that: "TCDD is a potent inducer of hepatic and renal microsomal drug metabolizing enzymes (Beatty and Neal, 1976; Buu-Hoi, et al.1971, 1972b; Fowler, et al. 1975; Greig, 1972; Greig and DeMatteis, 1973; Hook, et al. 1975 a,b; Lucier, et al. 1973, 1975a,b; Woods, 1973). Intoxication with TCDD results in a marked increase in the cellular smooth endoplasmic reticulum content of hepatic and renal cells (Fowler, et al. 1973, 1975). TCDD can

simultaneously activate and suppress certain microsome-associated foreign-compound- and steroid-hormone-metabolizing enzyme systems (Hook, et al. 1975a). It increased the activity of both renal and hepatic glutathione-S transferase, an enzyme that converts several organic compounds to metabolites that are transported by the proximal tubules of the kidney (Kirsch, et al. 1975).

TCDD is the most active of the chlorinated dibenzo-para-dioxins in inducing hepatic w-aminolevulinic acid (ALA) synthetase and aryl hydrocarbon hydroxylase (AHH) in chick embryo liver preparations (Poland and Glover, 1973a,b).

All of the chlorinated dibenzo-para-dioxins that induce ALA synthetase in chick embryo have two common properties: (1) halogen atoms occupy at least 3 of the 4 ring positions (2,3,7,8), and (2) there is at least one free, non-halogenated carbon atom (Poland and Glover, 1973b). The available toxicological data (Schwetz, et al. 1973) indicate that all those chlorodibenzo-para-dioxins that are lethal at low doses, teratogenic or produce acne also induce ALA synthetase; those chlorodibenzo-para-dioxins that are not toxic do not induce ALA synthetase. The structure-activity relationship of chlorodibenzo-para-dioxins in their ability to induce AHH in chick embryo was identical to that in inducing ALA synthetase (Poland and Glover, 1973b).

Mixed function oxidase enzyme systems of mouse strains 'non-responsive' to other aromatic hydrocarbons were induced by single doses of TCDD, as evidenced by increases in hepatic monooxygenase activities and in concentrations

of cytochrome P-448 (Chhabra, et al. 1974; Kouri and Nebert, 1977; Nebert, et al. 1975; Poland, et al. 1974). Genetic resistance to induction of AHH by 3-methylcholanthrene in DBA/2J mice was overcome by treatment with TCDD. This result conflicts with the hypothesis that induction of AHH activity is a consequence of the formation of cytochrome P-448 (Chhabra, et al. 1976). A component that has a high binding affinity for TCDD was found in mouse liver cytosol (Poland, et al. 1976).

TCDD induces AHH even in poorly responsive strains of mice (Niwa, et al. 1975a), not only in liver but also in lung, kidney and colon. The DBA/2N strain, which responds only weakly to the sarcomatogenic action of 3-methylcholanthrene, becomes highly susceptible after treatment with TCDD (Kouri, 1976; Kouri and Nebert, 1977).

TCDD is approximately 30,000 times more potent than 3-methylcholanthrene in inducing AHH activity in rat liver (Poland and Glover, 1974).

AHH activity in maternal and fetal livers was increased 14- and 100-fold, but only minimal increases were observed in placentas and adrenal glands following single administrations of 2.5-6.0 μg/kg of body weight of TCDD to Sprague-Dawley rats on day 17 of gestation. Similar results were obtained with regard to rates of 7-, 5-, N-, 3- and 1-hydroxylations of N-2-fluorenylacetamide. Benzo(a)pyrene metabolism to diols was also increased in fetal and maternal livers after treatment with TCDD, possibly by an increase in epoxide hydratase activity (Berry, et al. 1976).

The kinetics of TCDD induction of AHH in 10 established cell lines, the primary fetal cultures derived from hamsters, rats, rabbits, chicks and 4 inbred strains of mice and in cultured human lymphocytes were similar to those of hydroxylase induction by 3-methylcholanthrene. There was no relationship between the cytotoxicity of TCDD and the level of inducible hydroxylase activity in the cultures (Niwa, et al. 1975b).

The concentration of TCDD in growth medium necessary to induce AHH activity in cultured lymphocytes is 40-60 times less than that of 3-methylcholanthrene needed for maximal hydroxylase induction (Kouri, et al. 1974).

Carcinogenesis. Three studies have been reported concerning the carcinogenesis of TCDD in either the rat or the mouse (Van Miller, et al. 1977; Kociba, et al. In press; Toth, et al. 1977).

Male Sprague-Dawley rats were fed dietary levels of TCDD of 0, 0.001, 0.005, 0.05 or 0.5 µg/kg of diet or 1, 5, 50, 500, or 1,000 µg/kg of diet (Van Miller, et al. 1977). Ten rats were maintained at each concentration. The corresponding daily dosages in µg/kg of body weight (U.S. EPA, 1978) were 0, 0.00004, 0.0014, 0.0143, 0.057, 0.286, 3.43, 34.3, or 71.4 µg/kg of body weight. The rats receiving dietary levels of 50 µg/kg or more died between the second and fourth weeks of treatment. The control rats and those fed a dietary level of 0.0001 µg/kg did not get any tumors. At the end of 65 weeks, exploratory laparotomies were performed on all surviving rats and biopsies were taken from all tumors observed. Dosing of the rats then continued to 78 weeks at which time the animals were trans-

ferred to a control diet until they were sacrificed at 95 weeks and complete necropsies performed.

An incidence of 13 benign and 15 malignant tumors was observed among the 50 animals receiving TCDD at levels from 5 ng/kg of diet to 5 μg/kg of diet. The results and a description of the tumors found are given in Table 2. Neoplastic nodules and/or cholanglocarcinomas of the liver were observed in 5 animals. Forty percent (4/10) of the rats ingesting 5 μg/kg of TCDD had these lesions with two of the animals having both. One (10 percent) of the rats in the 1 μg/kg group had an hepatic carcinoma. No tumors were found in the controls.

The total number of tumors occurring at each dose level (Table 2) does not seem to follow a typical dose-response pattern. The reason for this is unknown. (Van Miller, et al. 1977).

Several experiments have been performed using random-bred Swiss H/Riop mice with various doses of TCDD (Toth, et al. 1977). Gastric intubation of 7 μg/kg of body weight of TCDD in sunflower oil were given weekly to 50 10-week-old males for 12 months. No tumors were observed in 19 autopsied mice but three had cirrhosis of the liver and eight had dermatitis and amyloidosis. The cummulative dose for the year (364 μg/kg of body weight) is more than three times the LD_{50} for male mice of 114 μg/kg of body weight (Vos, et al. 1974). Twelve months of dosing other rats with 0.7 μg/kg of body weight and 0.007 μg/kg of body weight of TCDD resulted in no significant changes 2 months after the end of treatment. The surviving mice are to be observed until their death.

Dose levels of 0, 0.1, 0.01, and 0.001 μg/kg of body weight of TCDD were studied for a 2-year period in three groups of 100 rats (50 of each sex) and a control group of 172 (86 of each sex) (Kociba, et al. In press).

Male rats at the 0.1 μg/kg of body weight TCDD dose exhibited a statistically significant increased incidence of squamous cell carcinomas of the hard palate (4 out of 50) and of the tongue (3 out of 50) than the controls which exhibited no carcinomas (0 out of 85). The female rats at the 0.1 μg/kg of body weight TCDD dose had a statistically significant increase in incidence of carcinomas at three sites, squamous cell carcinoma of the hard palate (4 out of 49) squamous cell carcinoma of the lung (7 out of 40), and hepatocellular carcinoma of the liver (11 out of 49). Only one carcinoma of these three sites occurred in the 86 controls and that was an hepatacellular carcinoma of the liver. Five sites, pancreas, adrenal gland, pituitary gland, uterus, and mammary gland, had a statistically significant decrease in their tumor incidence at certain dose levels (Kociba, et al. In press).

CRITERION FORMULATION

Existing Guidelines and Standards

There are no existing guidelines or standards other than a calculated acceptable daily intake (ADI) of 10^{-4} µg/kg/day for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The data base for the calculation did not consider TCDD to be a known or suspect carcinogen (NRC, Drinking Water and Health). Although TCDD is a contaminant of some chlorinated herbicides, there are no tolerances for TCDD in or on food crops. 40 CFR 180.302 does, however, establish a tolerance of 0.05 ppm hexachlorophene in or on cotton seed (a non-human dietary food item) and states that technical grade hexachlorophene shall not contain more than 0.1 ppm TCDD.

Current Levels of Exposure

The amount of human exposure to TCDD that can be directly attributed to water cannot be determined. TCDD is believed not to occur naturally in the environment. However, a recent study by the Dow organized "chlorinated dioxin task force" (Chemical and Engineering News, Nov. 20, 1978) reported that chlorinated dioxins, including TCDD, "were found in every sample of particulate matter taken from the air emissions of a wide variety of commercial and domestic combustion processes." The solubility of TCDD and its inability to vertically migrate through soil indicate that ground water would probably not be contaminated although run-off from soil treated with TCDD containing herbicides is not precluded.

The several reported incidencts of toxic manifestations of exposure to TCDD in factories and from accidental contamination via inhalation and/or dermal routes illustrate the toxicity of the compound. The levels and duration of exposure were not determinable in most cases.

Special Groups at Risk

A special group at risk would be workers in an industrial environment where exposure to TCDD-contaminated products is a possibility. A special sub-group at risk are women of childbearing age and children.

Basis and Derivation of Criterion

TCDD is an extremely toxic compound exhibiting acute, subchronic and chronic effects in animals and humans. The liver appears to be the target organ of acute exposure. Retention of TCDD by the liver indicates that it apparently undergoes little or no metabolism.

Acute effects of exposure include chloracne, porphyria cutanea tarda, hepatotoxicity, psychological alterations, weight loss, thymic atrophy, thrombocytopenia, suppression of cellular immunity and death. TCDD is teratogenic and fetotoxic. Oral exposure of pregnant rats to 0.125 to 2.0 ug TCDD/kg/day produced fetal mortality, fetal intestinal hemorrhage and both early and late resorptions. Smith, et al. (1976) found an increased incidence of cleft palate when pregnant mice were given TCDD doses of 1.0 µg/kg/day for 10 days during gestation.

TCDD has been shown to be mutagenic in three bacterial systems (Hussain, 1972) and a potent inducer of hepatic and renal microsomal drug metabolizing enzymes (IARC).

The carcinogenic potential of tetrachlorodibenzo-p-dioxin has been established by the findings of two feeding studies. The studies are: The Van Miller et al., feeding of two feeding study in Sprague-Dawley rats at dose levels from 5 ppt to ppb which revealed a significant excess of tumors in TCDD treated rats as compared to the controls (see Table 2 in the document). Another feeding study, conducted by Kociba, et al. (In press) using the same strain of rats at 0.1, 0.01, 0.001 μg/kg/day, induced a statistically significant excess of hepatocellular carcinoma in treated rats. Based on these two studies, tetrachlorodibenzo-p-dioxin is likely to be a human carcinogen.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." TCDD is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of TCDD in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of TCDD corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of

the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availabilty of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6} of 10^{-7} as shown in the following table.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish.	0 (2)	4.55×10^{-9}	4.55×10^{-8}	455×10^{-7} ug/l
Consumption of fish and shellfish only.	0	4.63×10^{-9}	4.63×10^{-8}	4.63×10^{-7} ug/l

(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document of the document to the animal bioassay data presented in Appendix I of the document. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) Approximately 98 percent of the TCDD exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 5,800-fold. The remaining 2 percent of TCDD exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of TCDD, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding TCDD concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding TCDD concentrations. Because data indicating other sources of TCDD exposure and their contributions to total body burden are inadequate for quantitative use, the figures reflect the incremental risks associated with the indicated routes only.

Table 1. - Lethal Dose 50 concentrations for various animals

Species and Sex	Route of Administrations	LD50 ug/kg	Reference
Rat, male	Oral	22	Schwetz, et al. 1973
Rat, female	Oral	45	Schwetz, et al. 1973
Mice, male	Oral	114	Vos, et al. 1974
Guinea pig, male	Oral	0.6	Schwetz, et al. 1973
Guinea pig, male	Oral	2.1	Schwetz, et al. 1973
Rhesus monkey, female	Oral	< 70	McConnell, et al. 1975
Rabbitt, mixed	Oral	115	Schwetz, et al. 1973
Rabbitt, mixed	Skin	275	Schwetz, et al. 1973
Rabbitt, mixed	Oral	10	Schulz, 1968

Table 2. - Number of tumors occurring in male rats ingesting TCDD

Dosage	Tumors			Rats with tumors	
	Benign	Malignant	Total	No.	Percent
0	0	0	0	0/10	0
1 ppt	0	0	0	0/10	0
5 ppt	1	5	6[a]	5/10	50[b]
50 ppt	2	1	3[c]	3/10	30
500 ppt	2	2	4[d]	4/10	40[e]
1 ppb	0	5	5[f]	4/10	40
5 ppb	8	2	10[g]	7/10	70

Data from Van Miller (1977)

ppt = parts per trillion; ppb = parts per billion

[a]One rat had both lympocytic leukemia and a carcinoma of the ear duct. The other four rats had respecitvely, adenocarcinomas of the kidney, retroperitoneal malignant histiocytoma, skin angiosarcoma, and Leydig cell adenoma of the testes.

[b]Three rats died with aplastic anemia.

[c]Three rats had muscle fibrosarcoma, squamous cell tumor of the skin, and astrocytoma of the brain, respectively.

[d]Four rats had striated muscle fibroma, skin carcinoma, sclerosing seminoma of a testis, and kidney adenocarcinoma, respectively.

[e]One rat had a severe infarction of the liver.

[f]One rat had both cholangiocarcinoma and retroperitoneal histiocytomas. The remaining three rats had skin angiosarcoma, glioblastoma of the brain and retroperitoneal malignant histiocytoma, respectively.

[g]One rat had both a squamous cell tumor of the lung and a neoplastic nodule of the liver. Two rats had both cholangiocarcinoma and neoplastic nodules of the liver. Three rats had squamous cell tumors of the lung and one rat had a neoplastic nodule of the liver.

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APPENDIX I

Derivation of Criterion for Dioxin

A study of Sprague-Dawley rats in which dioxin was added to the diet at a concentration of 0.1 μg/kg/day for 2 years resulted in hepatocellular carcinoma in 11 of 49 treated females whereas only 1 of 86 controls had hepatocellular carcioma (Kociba, et al. In press). Using a bioaccumulation factor 5,800 the parameters of the extrapolation model are:

$n_t = 11$	le = 24 months
$N_t = 49$	$d = 10^{-4}$ mg/kg/day
$n_c = 1$	w = 0.37 kg
$N_c = 86$	L = 24 months
Le = 24 months	R = 5,800

The result is that the water concentration should be less than 4.55×10^{-7} micrograms per liter in order to keep the individual lifetime risk below 10^{-5}.